

UTILITY APPLICATION

UNDER 37 CFR § 1.53(B)

TITLE: **5-CYCLOALKENYL 5-H-CHROMENO[3,4-f]QUINOLINE  
DERIVATIVES AS SELECTIVE PROGESTERONE  
RECEPTOR MODULATOR COMPOUNDS**

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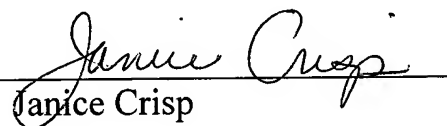
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of U.S. Provisional Patent Application Serial 60/417,975,  
filed October 11, 2002.

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**5-CYCLOALKENYL 5H-CHROMENO[3,4-f]QUINOLINE DERIVATIVES**  
**AS SELECTIVE PROGESTERONE RECEPTOR MODULATOR**  
**COMPOUNDS**

5

**Related Applications**

This application claims the benefit of priority of U.S. Provisional Application Ser. No. 60/417,975 filed October 11, 2002, the entire disclosure of which is incorporated herein by reference.

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**Field of the Invention**

This invention relates to nonsteroidal 5-cycloalkenyl 5H-chromeno[3,4-f]quinoline derivatives that may be modulators (*i.e.*, agonists, partial agonists and antagonists) of progesterone receptors and to methods for the making and use of such compounds.

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**Background of the Invention**

Progesterone receptor (PR) modulators have been widely used in regulation of female reproduction systems and in treatment of female hormone dependent diseases. The effectiveness of known steroidal PR modulators is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of synthetic progestins, such as norgestrel, as female birth control agents must be weighed against the increased risk of breast cancer and heart disease. Similarly, the progesterone antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a

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patient due to its inherent cross-reactivity as a glucocorticoid receptor (GR) antagonist. Accordingly, identification of compounds that have good receptor-selectivity for PR over other steroid hormone receptors as well as good tissue-selectivity (e.g., selectivity for uterine tissue over breast tissue) would be of  
5 significant value in the improvement of women's health.

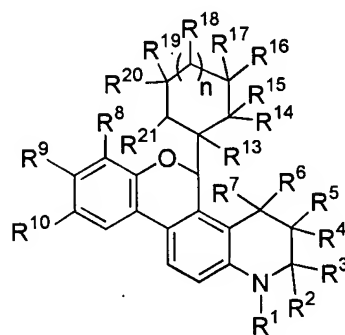
A group of nonsteroidal molecules, which contain a di- or tetra-hydroquinoline ring as core pharmacophore (U.S. Patent Nos. 5,693,646; 5,693,647 and 5,696,127; PCT Int'l. Publication Nos. WO 99/41256 A1 and WO 99/41257 A1) have been described as steroid receptor modulator compounds.

10 The entire disclosures of the patents, publications and references referred to herein are incorporated by reference herein and are not admitted to be prior art.

### **Summary of the Invention**

The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone  
15 Receptor. More particularly, the invention relates to nonsteroidal compounds and compositions which may be high affinity, high specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and/or antagonists for progesterone receptors. Also provided are methods of making such compounds and pharmaceutical compositions.

Compounds of the present invention may be represented by the formulae:



(I)

wherein:

5  $R^1$  is selected from the group of hydrogen,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl,  $C_1-C_4$  heteroalkyl,  $COR^{11}$ ,  $CO_2R^{11}$ ,  $SO_2R^{11}$ , and  $CONR^{11}R^{12}$ ;

$R^2$  and  $R^3$  each independently is selected from the group of hydrogen,  $C_1-C_6$  alkyl, and  $C_1-C_6$  haloalkyl; or

10  $R^2$  and  $R^3$  taken together form a cycloalkyl ring of from three to twelve carbons;

$R^4$  through  $R^7$  each independently is selected from the group of hydrogen, F, Cl, Br, CN,  $OR^{11}$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl, and  $C_1-C_4$  heteroalkyl; or

$R^5$  and  $R^7$  taken together form a bond; or

15  $R^6$  and  $R^7$  taken together are selected from the group of methyldene, mono-substituted methyldene, di-substituted methyldene and carbonyl;

$R^8$  through  $R^{10}$  each independently is selected from the group of hydrogen, F, Cl, Br, I,  $\text{NO}_2$ , CN,  $\text{OR}^{11}$ ,  $\text{NR}^{11}\text{R}^{12}$ ,  $\text{SR}^{11}$ ,  $\text{COR}^{11}$ ,  $\text{CO}_2\text{R}^{11}$ ,  $\text{CONR}^{11}\text{R}^{12}$ ,  $\text{C}_1\text{--C}_8$  alkyl,  $\text{C}_1\text{--C}_8$  heteroalkyl,  $\text{C}_1\text{--C}_8$  haloalkyl, allyl,  $\text{C}_2\text{--C}_8$  alkenyl,  $\text{C}_2\text{--C}_8$  alkynyl;

$R^{11}$  and  $R^{12}$  each is independently selected from the group of hydrogen,  $\text{C}_1\text{--C}_4$  alkyl,  $\text{C}_1\text{--C}_4$  heteroalkyl, and  $\text{C}_1\text{--C}_4$  haloalkyl;

$R^{13}$  is hydrogen; or

$R^{13}$  and  $R^{14}$  taken together form a bond;

$R^{14}$  through  $R^{20}$  each independently is selected from the group of hydrogen, F, Cl, Br,  $\text{OR}^{11}$ ,  $\text{C}_1\text{--C}_4$  alkyl,  $\text{C}_1\text{--C}_4$  haloalkyl, and  $\text{C}_1\text{--C}_4$  heteroalkyl; or

$R^{14}$  and  $R^{15}$  taken together are selected from the group of methylenide, carbonyl and thiocarbonyl; or

$R^{16}$  and  $R^{17}$  taken together are selected from the group of methylenide, mono-substituted methylenide, di-substituted methylenide, ethylenide, carbonyl and thiocarbonyl; or

$R^{14}$  and  $R^{16}$  taken together form a bond or “—O—” bridge; or

$R^{16}$  and  $R^{18}$  taken together form a bond when n is 1; or

$R^{16}$  and  $R^{19}$  taken together form a bond when n is 0;

$R^{21}$  is hydrogen; or

$R^{21}$  and  $R^{20}$  taken together form a bond;

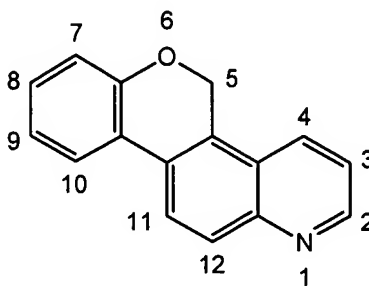
n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

### **Definitions and Nomenclature**

5           As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such  
10   compounds is also provided.

A 5*H*-chromeno[3,4-*f*]quinoline is defined by the following structure:



The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain or cyclic-chain alkyl radical having from 1 to about  
15   12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having

from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

The term “alkenyl,” alone or in combination, refers to an optionally  
5 substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals  
10 include ethenyl, propenyl, 1,3-butadienyl and the like.

“Methyldene,” alone or in combination, refers to  $=CH_2$  and may be optionally substituted.

“Allyl,” alone or in combination, refers to  $-CH_2-CH=CH_2$  and may be optionally substituted.

15 The term “alkynyl,” alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon triple bonds and having from 2 to about 6 carbon atoms as  
20 well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals

include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl," "heteroalkenyl" and "heteroalkynyl" refer to alkyl, alkenyl and alkynyl radicals, respectively, as described above, in which one or more skeletal atoms are heteroatoms such as, for example, oxygen, nitrogen, sulfur or combinations thereof. The terms heteroalkyl, heteroalkenyl and heteroalkynyl include radicals in which 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

10 The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from to six about twenty carbon atoms. The term aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from six to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl radicals include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

20 The term "heteroaryl" refers to an optionally substituted aromatic ring system containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term



heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (*e.g.*, a six membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinoliny, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indoliziny, thienyl and the like.

The terms haloalkyl, haloalkenyl, haloalkynyl and haloalkoxy include alkyl, alkenyl, and alkynyl structures, as described above, that are substituted with one or more fluorines, chlorines, bromines or iodines, or with combinations thereof.

The terms cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl include optionally substituted cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl radicals.

The term "carbocycle" includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which all of the skeletal

atoms are carbon.

The term “heterocycle” includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which one or more skeletal atoms is oxygen, nitrogen, sulfur, or combinations thereof.

5       The term “acyl” includes alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituents attached to a compound via a carbonyl functionality (*e.g.*, -CO-alkyl, -CO-aryl, -CO-arylalkyl or -CO-heteroarylalkyl, etc.).

The term “halogen” includes F, Cl, Br and I.

10       The term “mediate” means affect or influence, frequently indirectly or via some intervening action. Thus, for example, conditions mediated by a progesterone receptor are those in which a progesterone receptor plays a role. Progesterone receptors are known to play a role in conditions including, for example, infertility, contraception, pregnancy maintenance and termination, female hormone deficiency, female sexual dysfunction, dysfunctional uterine bleeding, endometriosis, mood  
15       disorder, osteoporosis, and hormone-dependent cancers.

20       The term “receptor-selectivity” refers to the conditions where a compound displays modulating activity towards one or more particular receptors (*e.g.*, a progesterone receptors) while displaying substantially less or no cross-reactivity towards one or more different receptors (*e.g.*, glucocorticoid receptors). Thus, for example, selective compounds of the present invention may display modulating

activity towards progesterone receptors without displaying substantial cross-reactivity towards another steroid hormone receptors. Compounds may be selective for a single receptor, group of similar receptors or multiple receptors.

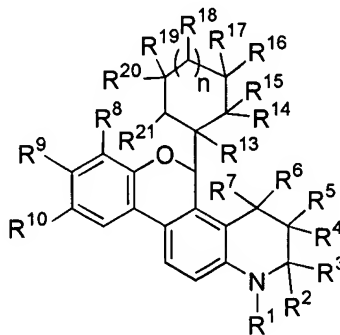
The term “tissue-selectivity” refers to compounds that display substantial  
5 modulating activity in one tissue (*e.g.*, uterine tissue) while displaying lesser  
modulating activity in at least one other tissue (*e.g.*, breast tissue). Thus, for  
example, tissue-selective compounds of the present invention may display  
substantial modulating activity in uterine and vaginal tissues with lesser modulating  
activity (partial agonistic or partial antagonistic) in breast tissues relative to the  
10 activities of the marketed steroidal progestins in all of the target tissues.

The term “modulate” means affect or influence, for example, the amount,  
degree or proportion. Thus, compounds that “modulate” a receptor affect the  
activity, either positively or negatively, of that receptor. The term may be used to  
refer to the activity of compounds of a receptor as, for example, an agonist, partial  
15 agonist or antagonist. The term also may be used to refer to the effect that a  
compound has on a physical and/or physiological condition of an individual. For  
example, certain compounds of the present invention may be used to modulate  
fertility in an individual. That is, certain compounds of this invention may be used  
to increase the fertility of an individual, while other compounds of this invention  
20 may be used to decrease the fertility of an individual.

A compound that binds to a receptor and mimics the effect of the native or endogenous ligand is referred to as an "agonist," while a compound that binds to a receptor and inhibits or has an effect that is opposite that of the native or endogenous ligand is called an "antagonist." "Partial agonists" give an effect of the same type as the native or endogenous ligand, but of a lower magnitude, while "partial antagonists" are incompletely inhibitory or opposite that of the native or endogenous ligand.

### Detailed Description of the Invention

Compounds of the present invention may be represented by the formulae:



10

(I)

wherein:

$R^1$  is selected from the group of hydrogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $C_1$ - $C_4$  heteroalkyl,  $COR^{11}$ ,  $CO_2R^{11}$ ,  $SO_2R^{11}$ , and  $CONR^{11}R^{12}$ ;

15

$R^2$  and  $R^3$  each independently is selected from the group of hydrogen,  $C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  haloalkyl; or

$R^2$  and  $R^3$  taken together form a cycloalkyl ring of from three to twelve carbons;

$R^4$  through  $R^7$  each independently is selected from the group of hydrogen, F, Cl, Br, CN,  $OR^{11}$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl, and  $C_1-C_4$  heteroalkyl; or

5  $R^5$  and  $R^7$  taken together form a bond; or

$R^6$  and  $R^7$  taken together are selected from the group of methyldiene, mono-substituted methyldiene, di-substituted methyldiene and carbonyl;

$R^8$  through  $R^{10}$  each independently is selected from the group of hydrogen, F, Cl, Br, I,  $NO_2$ , CN,  $OR^{11}$ ,  $NR^{11}R^{12}$ ,  $SR^{11}$ ,  $COR^{11}$ ,  $CO_2R^{11}$ ,  $CONR^{11}R^{12}$ ,  $C_1-C_8$  alkyl,  
10  $C_1-C_8$  heteroalkyl,  $C_1-C_8$  haloalkyl, allyl,  $C_2-C_8$  alkenyl and  $C_2-C_8$  alkynyl;

$R^{11}$  and  $R^{12}$  each is independently selected from the group of hydrogen,  $C_1-C_4$  alkyl,  $C_1-C_4$  heteroalkyl, and  $C_1-C_4$  haloalkyl;

$R^{13}$  is hydrogen; or

$R^{13}$  and  $R^{14}$  taken together form a bond;

15  $R^{14}$  through  $R^{20}$  each independently is selected from the group of hydrogen, F, Cl, Br,  $OR^{11}$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl, and  $C_1-C_4$  heteroalkyl; or

$R^{14}$  and  $R^{15}$  taken together are selected from the group of methyldiene, carbonyl and thiocarbonyl; or

$R^{16}$  and  $R^{17}$  taken together are selected from the group of methyldene, mono-substituted methyldene, di-substituted methyldene, ethyldene, carbonyl and thiocarbonyl; or

$R^{14}$  and  $R^{16}$  taken together form a bond or “-O-” bridge; or

5  $R^{16}$  and  $R^{18}$  taken together form a bond when n is 1; or

$R^{16}$  and  $R^{19}$  taken together form a bond when n is 0;

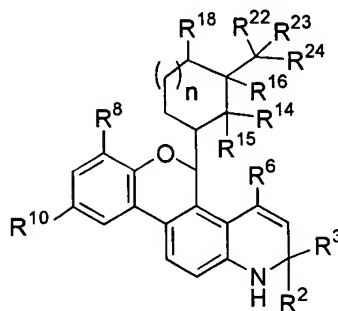
$R^{21}$  is hydrogen; or

$R^{21}$  and  $R^{20}$  taken together form a bond;

n is 0, 1, 2, or 3;

10 and pharmaceutically acceptable salts and prodrugs thereof.

Compounds of the invention include those represented by the formulae:



(II)

wherein:

$R^2$  and  $R^3$  each independently is selected from the group of hydrogen,  $C_1$ – $C_4$  alkyl, and  $C_1$ – $C_4$  haloalkyl;

$R^6$  is selected from the group of hydrogen, F, Cl, Br, CN,  $OR^{11}$ ,  $C_1$ – $C_4$  alkyl, and  $C_1$ – $C_4$  haloalkyl;

- 5         $R^8$  and  $R^{10}$  each independently is selected from the group of hydrogen, F, Cl, Br, CN,  $OR^{11}$ ,  $NR^{11}R^{12}$ ,  $SR^{11}$ ,  $COR^{11}$ ,  $C_1$ – $C_4$  alkyl,  $C_1$ – $C_4$  heteroalkyl,  $C_1$ – $C_4$  haloalkyl, allyl, and  $C_2$ – $C_4$  alkenyl;

$R^{11}$  and  $R^{12}$  each is independently selected from the group of hydrogen,  $C_1$ – $C_4$  alkyl,  $C_1$ – $C_4$  heteroalkyl, and  $C_1$ – $C_4$  haloalkyl;

- 10         $R^{14}$ ,  $R^{15}$ ,  $R^{18}$ ,  $R^{22}$ ,  $R^{23}$ ,  $R^{24}$  each independently is selected from the group of hydrogen, F, Cl,  $OR^{11}$ ,  $C_1$ – $C_4$  alkyl,  $C_1$ – $C_4$  haloalkyl, and  $C_1$ – $C_4$  heteroalkyl;

$R^{22}$ ,  $R^{23}$ ,  $R^{24}$  together consists of not more than 3 carbon atoms;

$R^{16}$  taken together with one of  $R^{14}$ ,  $R^{18}$ , and  $R^{22}$  form a bond or “–O–” bridge;

- 15        n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

In the following table, the inventors contemplate any combination of the following Markush groups and those described above for the various variables.

**Table A. Table of Markush Groups by Variable**

	<b>Markush Group A</b>	<b>Markush Group B</b>	<b>Markush Group C</b>	<b>Markush Group D</b>
R <sup>1</sup>	H, C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl, C <sub>1</sub> -C <sub>4</sub> heteroalkyl, COR <sup>11</sup> , CO <sub>2</sub> R <sup>11</sup> , SO <sub>2</sub> R <sup>11</sup> and CONR <sup>11</sup> R <sup>12</sup>	H, C <sub>1</sub> -C <sub>4</sub> alkyl, COR <sup>11</sup> , SO <sub>2</sub> R <sup>11</sup> and CONR <sup>11</sup> R <sup>12</sup>	H and methyl	H
R <sup>2</sup>	H, C <sub>1</sub> -C <sub>6</sub> alkyl and C <sub>1</sub> -C <sub>6</sub> haloalkyl	C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and methyl	H
	R <sup>2</sup> and R <sup>3</sup> taken together form a C <sub>3</sub> -C <sub>12</sub> cycloalkyl ring	R <sup>2</sup> and R <sup>3</sup> taken together form a C <sub>4</sub> -C <sub>10</sub> cycloalkyl ring	R <sup>2</sup> and R <sup>3</sup> taken together form a C <sub>6</sub> -C <sub>8</sub> cycloalkyl ring	R <sup>2</sup> and R <sup>3</sup> taken together form a C <sub>5</sub> -C <sub>6</sub> cycloalkyl ring
R <sup>3</sup>	H, C <sub>1</sub> -C <sub>6</sub> alkyl and C <sub>1</sub> -C <sub>6</sub> haloalkyl	C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and methyl	H
R <sup>4</sup>	H, F, Cl, Br, CN, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F, OR <sup>11</sup> and C <sub>1</sub> -C <sub>4</sub> alkyl	H, F and methyl	H
R <sup>5</sup>	H, F, Cl, Br, CN, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl, and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F and C <sub>1</sub> -C <sub>4</sub> alkyl	H, F and methyl	H
	R <sup>5</sup> and R <sup>7</sup> taken together form a bond			



	<b>Markush Group A</b>	<b>Markush Group B</b>	<b>Markush Group C</b>	<b>Markush Group D</b>
$R^6$	H, F, Cl, Br, CN, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl, and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F, Cl, Br, CN, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and C <sub>1</sub> -C <sub>4</sub> alkyl	methyl
	$R^6$ and $R^7$ taken together form a methylenide, mono-substituted methylenide, di-substituted methylenide or carbonyl	$R^6$ and $R^7$ taken together form a methylenide or carbonyl		$R^6$ and $R^7$ taken together form a methylenide
$R^7$	H, F, Cl, Br, CN, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H, F and methyl	H and F
	$R^5$ and $R^7$ taken together form a bond			
	$R^6$ and $R^7$ taken together form a methylenide, mono-substituted methylenide, di-substituted methylenide or carbonyl	$R^6$ and $R^7$ taken together form a methylenide or carbonyl	$R^6$ and $R^7$ taken together form a carbonyl	$R^6$ and $R^7$ taken together form a methylenide

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R <sup>8</sup>	H, F, Cl, Br, I, NO <sub>2</sub> , CN, OR <sup>11</sup> , NR <sup>11</sup> R <sup>12</sup> , SR <sup>11</sup> , COR <sup>11</sup> , CO <sub>2</sub> R <sup>11</sup> , CONR <sup>11</sup> R <sup>12</sup> , C <sub>1</sub> -C <sub>8</sub> alkyl, C <sub>1</sub> -C <sub>8</sub> heteroalkyl, C <sub>1</sub> -C <sub>8</sub> haloalkyl, allyl, C <sub>2</sub> - C <sub>8</sub> alkenyl and C <sub>2</sub> - C <sub>8</sub> alkynyl	H, F, Cl, Br, NO <sub>2</sub> , CN, OR <sup>11</sup> , SR <sup>11</sup> , C <sub>1</sub> -C <sub>6</sub> alkyl, C <sub>1</sub> -C <sub>6</sub> heteroalkyl, and C <sub>1</sub> - C <sub>6</sub> haloalkyl	H, F, and OR <sup>11</sup>	H
R <sup>9</sup>	H, F, Cl, Br, I, NO <sub>2</sub> , CN, OR <sup>11</sup> , NR <sup>11</sup> R <sup>12</sup> , SR <sup>11</sup> , COR <sup>11</sup> , CO <sub>2</sub> R <sup>11</sup> , CONR <sup>11</sup> R <sup>12</sup> , C <sub>1</sub> -C <sub>8</sub> alkyl, C <sub>1</sub> -C <sub>8</sub> heteroalkyl, C <sub>1</sub> -C <sub>8</sub> haloalkyl, allyl, C <sub>2</sub> - C <sub>8</sub> alkenyl and C <sub>2</sub> - C <sub>8</sub> alkynyl	H, F, Cl, Br, NO <sub>2</sub> , CN, OR <sup>11</sup> , SR <sup>11</sup> , C <sub>1</sub> -C <sub>6</sub> alkyl, C <sub>1</sub> -C <sub>6</sub> heteroalkyl, and C <sub>1</sub> - C <sub>6</sub> haloalkyl	H, F, and OR <sup>11</sup>	H
R <sup>10</sup>	H, F, Cl, Br, I, NO <sub>2</sub> , CN, OR <sup>11</sup> , NR <sup>11</sup> R <sup>12</sup> , SR <sup>11</sup> , COR <sup>11</sup> , CO <sub>2</sub> R <sup>11</sup> , CONR <sup>11</sup> R <sup>12</sup> , C <sub>1</sub> -C <sub>8</sub> alkyl, C <sub>1</sub> -C <sub>8</sub> heteroalkyl, C <sub>1</sub> -C <sub>8</sub> haloalkyl, allyl, C <sub>2</sub> - C <sub>8</sub> alkenyl and C <sub>2</sub> - C <sub>8</sub> alkynyl	H, F, Cl, Br, NO <sub>2</sub> , CN, OR <sup>11</sup> , SR <sup>11</sup> , C <sub>1</sub> -C <sub>6</sub> alkyl, C <sub>1</sub> -C <sub>6</sub> heteroalkyl and C <sub>1</sub> - C <sub>6</sub> haloalkyl	H, F, and OR <sup>11</sup>	F
R <sup>11</sup>	H, C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> - C <sub>4</sub> heteroalkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and C <sub>1</sub> -C <sub>4</sub> alkyl	H and C <sub>1</sub> -C <sub>2</sub> alkyl	H
R <sup>12</sup>	H, C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> - C <sub>4</sub> heteroalkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and C <sub>1</sub> -C <sub>4</sub> alkyl	H and C <sub>1</sub> -C <sub>2</sub> alkyl	H

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R <sup>13</sup>	H			
	R <sup>13</sup> and R <sup>14</sup> taken together form a bond			
R <sup>14</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F, Cl, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H, F, C <sub>1</sub> -C <sub>2</sub> alkyl, and C <sub>1</sub> -C <sub>2</sub> haloalkyl	H
	R <sup>13</sup> and R <sup>14</sup> taken together form a bond			
	R <sup>14</sup> and R <sup>15</sup> taken together form a methyldene, carbonyl or thiocarbonyl	R <sup>14</sup> and R <sup>15</sup> taken together form a methyldene or carbonyl		R <sup>14</sup> and R <sup>15</sup> taken together form a methyldene
	R <sup>14</sup> and R <sup>16</sup> taken together form a bond or “-O-” bridge		R <sup>14</sup> and R <sup>16</sup> taken together form a “-O-” bridge	R <sup>14</sup> and R <sup>16</sup> taken together form a bond
R <sup>15</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F, Cl, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and C <sub>1</sub> -C <sub>4</sub> alkyl	H
	R <sup>14</sup> and R <sup>15</sup> taken together form a methyldene, carbonyl or thiocarbonyl	R <sup>14</sup> and R <sup>15</sup> taken together form a methyldene or carbonyl		R <sup>14</sup> and R <sup>15</sup> taken together form a methyldene

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R <sup>16</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> -C <sub>4</sub> heteroalkyl	H, F, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H, F, and C <sub>1</sub> -C <sub>4</sub> alkyl	H
	R <sup>14</sup> and R <sup>16</sup> taken together form a bond or “-O-” bridge		R <sup>14</sup> and R <sup>16</sup> taken together form a “-O-” bridge	R <sup>14</sup> and R <sup>16</sup> taken together form a bond
	R <sup>16</sup> and R <sup>17</sup> taken together form a methyldene, mono-substituted methyldene, di-substituted methyldene, ethyldene, carbonyl or thiocarbonyl	R <sup>16</sup> and R <sup>17</sup> taken together form a methyldene, mono-substituted methyldene, di-substituted methyldene, or ethyldene	R <sup>16</sup> and R <sup>17</sup> taken together form a methyldene or ethyldene	R <sup>16</sup> and R <sup>17</sup> taken together form a methyldene
	R <sup>16</sup> and R <sup>18</sup> taken together form a bond			
	R <sup>16</sup> and R <sup>19</sup> taken together form a bond			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R <sup>17</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> - <sub>4</sub> heteroalkyl	H, F, Cl, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H and C <sub>1</sub> -C <sub>2</sub> alkyl	methyl
	R <sup>16</sup> and R <sup>17</sup> taken together form a methylidene, mono-substituted methylidene, di- substituted methylidene, ethylidene, carbonyl or thiocarbonyl	R <sup>16</sup> and R <sup>17</sup> taken together form a methylidene, mono- substituted methylidene, di- substituted methylidene, or ethylidene	R <sup>16</sup> and R <sup>17</sup> taken together form a methylidene or ethylidene	R <sup>16</sup> and R <sup>17</sup> taken together form a methylidene
R <sup>18</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> - C <sub>4</sub> heteroalkyl	H, F, Cl, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H, F and C <sub>1</sub> -C <sub>4</sub> alkyl	H
	R <sup>16</sup> and R <sup>18</sup> taken together form a bond			
R <sup>19</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> - C <sub>4</sub> heteroalkyl	H, F, Cl, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H, F and C <sub>1</sub> -C <sub>4</sub> alkyl	H
	R <sup>16</sup> and R <sup>19</sup> taken together form a bond			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R <sup>20</sup>	H, F, Cl, Br, OR <sup>11</sup> , C <sub>1</sub> -C <sub>4</sub> alkyl, C <sub>1</sub> -C <sub>4</sub> haloalkyl and C <sub>1</sub> - C <sub>4</sub> heteroalkyl	H, F, Cl, C <sub>1</sub> -C <sub>4</sub> alkyl and C <sub>1</sub> -C <sub>4</sub> haloalkyl	H, F and C <sub>1</sub> -C <sub>2</sub> alkyl	H
	R <sup>21</sup> and R <sup>20</sup> taken together form a bond			
R <sup>21</sup>	H			
	R <sup>21</sup> and R <sup>20</sup> taken together form a bond			
n	0, 1, 2, or 3	0 or 1		1

In one aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a progesterone receptor modulator compound according to any one of formulae I through II shown above wherein R<sup>1</sup> through R<sup>24</sup>, and n all have the same definitions as given above.

In another aspect, the present invention comprises a method of modulating processes mediated by progesterone receptors comprising administering to a patient an effective amount of a compound according to any one of the formulae I through II shown above, wherein R<sup>1</sup> through R<sup>24</sup>, and n all have the same definitions as those given above.

Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical

compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, 5 formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

The PR agonist, partial agonist and antagonist compounds of the present invention may be particularly useful for female hormone replacement therapy and as 10 modulators of fertility (*e.g.*, as contraceptives, contragestational agents or abortifacients, *in vitro* fertilization, pregnancy maintenance), either alone or in conjunction with one or more estrogen receptor modulators. The PR modulator compounds of this invention may be also used in the treatment of dysfunctional 15 uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, and meningiomas. The PR modulator compounds of this invention also may be used in the treatment of various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, endometrium and prostate. The PR modulator compounds of this invention can also be used in treatment of 20 female osteoporosis, either alone or in combination with one or more estrogen receptor modulators.

It will be understood by those skilled in the art that while the compounds of the present invention will typically be employed as selective agonists, partial agonists or antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (*i.e.*,  
5 progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare ups that  
10 occur.

Furthermore, it will be understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus,  
15 the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

20 Representative PR modulator compounds (*i.e.*, agonists, partial agonists and antagonists) according to the present invention include:



(±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **24**);

(±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **25**);

5        (+)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **27**);

(-)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **28**);

10       (±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **29**);

(±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **30**);

(+)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **32**);

15       (-)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **33**);

(±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **34**);

- (±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 35);
- (+)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 37);
- 5        (-)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 38);
- (±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 39);
- (±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-10    5*H*-chromeno[3,4-*f*]quinoline (compound 41);
- (±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 42);
- (±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 44);
- 15        (±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 45);
- (±)-(5*l*,1'*l*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 47);

(±)-(5*l*,1'*u*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 48);

(±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 50);

5 (±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 51);

(±)-5-(3-methyl-3-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 52);

(±)-5-(2-cyclopenta-1,3-dienyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-  
10 chromeno[3,4-*f*]quinoline (compound 53);

(±)-(5*l*,1'*l*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 55);

(±)-(5*l*,1'*u*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 56);

15 (±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 58);

(±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 59);

(±)-(5*l*,1'*l*)-5-(3-ethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 61);

(±)-(5*l*,1'*l*)-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 62);

5 (±)-(5*l*,1'*l*)-5-(3-methyl-3-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 63);

(±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 64);

10 (±)-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 65);

(±)-(5*l*,1'*l*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 67);

(±)-(5*l*,1'*u*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 68);

15 (±)-5-(1-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 69);

(±)-(5*l*,1'*l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 71);

(+)-(5*l*,1'*l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 73);

(-)-(5*l*,1'*l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 74);

5       (±)-(5*l*,1'*l*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 75);

(±)-(5*l*,1'*u*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 76);

10       (±)-(5*l*,1'*l*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (compound 77);

(±)-(5*l*,1'*l*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 79);

(±)-(5*l*,1'*u*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 80);

15       (±)-(5*l*,1'*l*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 81);

(±)-(5*l*,1'*u*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 82);

(±)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-1,2,2,4-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 83);

(±)-5-(2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 84);

5 (±)-(5*l*,1'*l*)-5-(2,3-dimethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 85);

(±)-5-(3-methylidene-cyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 87);

10 (±)-(5*l*,1'*u*)-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound 88);

(±)-(5*l*,1'*l*)-5-(2-cycloheptenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 89);

(±)-(5*l*,1'*l*)-5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 91);

15 (±)-(5*l*,1'*u*)-5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 92);

(±)-(5*l*,1'*l*)-5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 94);

(±)-(5*l*,1'*l*)- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-  
2,2-dimethyl-4-methylene-5*H*-chromeno[3,4-*f*]quinolin-3-ol (Compound 95);

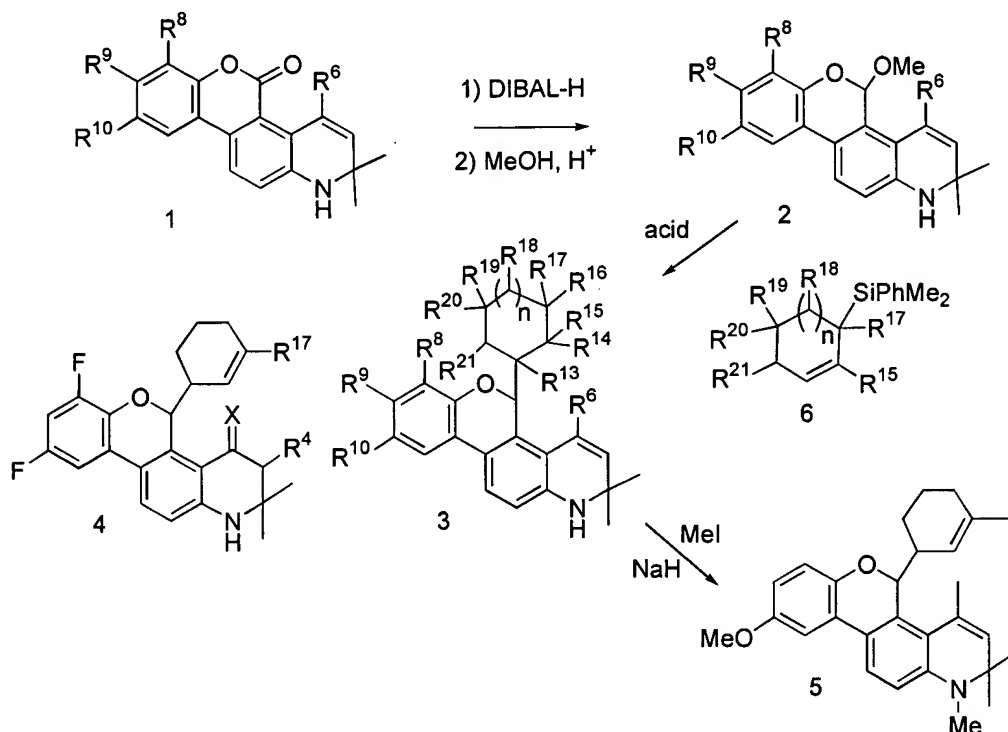
(±)-(5*l*,1'*l*)- 5-(2,3-epoxy-2,3-dimethylcyclopentyl)-7,9-difluoro-1,2-  
dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 96);

5 (±)-(5*l*,1'*u*)- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-  
2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 97); and

(±)-(5*l*,1'*l*)- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-  
2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinolin-4-one (Compound 98).

The sequence of steps for the general schemes to synthesize the compounds  
10 of the present invention is shown below. In each of the Schemes the R groups (*e.g.*,  
R<sup>1</sup>, R<sup>2</sup>, *etc.*) correspond to the specific substitution patterns noted in the Examples.  
However, it will be understood by those skilled in the art that other functionalities  
disclosed herein at the indicated positions of compounds of formulae I and II also  
comprise potential substituents for the analogous positions on the structures within  
15 the Schemes. In a further aspect, the present invention contains a novel process for  
the preparation of the compounds of the present invention.

**Scheme I**



Scheme I describes the synthesis of the 5-cycloalkenyl analogues 3, 4 and 5. Reduction of lactones 1, which were prepared by the previously disclosed methods (U.S. Patent Nos. 5,693,646; 5,693,647 and 5,696,127), with DIBAL-H followed by acid catalyzed methylation provides lactal intermediates 2. Treatment of the lactal 2 with a nucleophile, such as a cyclic allylsilane 6, in the presence of a Lewis acid, such as BF<sub>3</sub>-OEt<sub>2</sub>, affords the final product 3. Compound of structure 4 may also be isolated as a minor product. Methylation of compound 3 with iodomethane in the presence of a base, such as sodium hydride, provides N-methylated product of structure 5.



The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

5           As noted above, any of the PR modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and particularly in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide  
10   variety of forms depending upon the type of administration desired. Suitable administration routes include enteral (*e.g.*, oral), topical, suppository, inhalable and parenteral (*e.g.*, intravenous, intramuscular and subcutaneous).

          In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils,  
15   alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form  
20   for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be  
5 employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati,  
10 Ohio). Examples of suitable cream bases are Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention  
15 will generally be administered in the form of a dosage unit (*e.g.*, tablet, capsule, etc.). The compounds of the present invention generally are administered in a daily dosage of from about 1 µg/kg of body weight to about 50 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 2 µg/kg to about 25 mg/kg of body weight. Most often, the  
20 compounds of the present invention are administered in a daily dosage of from about 10 µg/kg to about 5 mg/kg body weight. As recognized by those skilled in the art,

the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

5           The compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR in a cell background or extract. They are particularly useful due to their ability to selectively activate progesterone receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related  
10   intracellular receptors.

          The compounds and pharmaceutical compositions of the present invention may be extremely potent activators of PR. For example, the compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 50 nM. Some compounds and compositions of the  
15   present invention may display 50% maximal activation of PR at a concentration of less than 20 nM, and some may display such activity at a concentration of less than 10 nM.

          The invention will be further illustrated by reference to the following non-limiting Examples.

**EXAMPLE 1**

Preparation of  $(\pm)$ -(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and  $(\pm)$ -(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline  
5 (Compounds **24** and **25**, Structure **3** of Scheme I, where  $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = F$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were prepared according to the following general procedure:

A mixture of a 5-methoxy-5*H*-chromeno[3,4-*f*]quinoline, such as 9-fluoro-2,2,4-trimethyl-5-methoxy-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline (compound  
10 **26**, Structure **2** of Scheme I, where  $R^8 = R^9 = H$ ,  $R^{10} = F$ ,  $R^6 = \text{methyl}$ ), and a cyclic allylsilane derivative, such as 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) (1.0-1.5 equiv.), in dry  $\text{CH}_2\text{Cl}_2$  was cooled to  $-25^\circ\text{C}$ , after which a Lewis acid such as  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (excess) was added dropwise. The resulting mixture was stirred at  
15  $-25^\circ\text{C}$  for half an hour, then warmed up gradually to  $0^\circ\text{C}$  and quenched with slow addition of aqueous  $\text{NaHCO}_3$  (concentrated). The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x). The extracts were washed with brine, combined, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc, 9:1) afforded 40-90% of a diastereomeric mixture of the 5-alkenyl  
20 products, which then were separated by prep TLC or HPLC.

Compound **24** was isolated as the major isomer:  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38 (d,  $J = 8.2$ , 1H), 7.29 (dt,  $J = 9.4$ , 3.1, 1H), 6.91 (dd,  $J = 8.6$ , 4.9, 1H), 6.82 (dt,  $J = 8.6$ , 3.1, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.64 (s, 1H), 5.52 (d,  $J = 14.0$ , 1H), 5.51 (s, 1H), 4.00 (s, 1H), 2.40 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.80 (m, 1H),  
5 1.64 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H), 1.28 (m, 1H), 1.22 (m, 1H), 1.14 (s, 3H), 1.06 (m, 1H).

Compound **25** was isolated as a minor isomer:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38 (d,  $J = 8.2$ , 1H), 7.29 (dt,  $J = 9.4$ , 3.1, 1H), 6.86 (m, 1H), 6.82 (m, 1H), 6.61 (dd,  $J = 8.2$ , 1.8, 1H), 5.63 (d,  $J = 10.1$ , 1H), 5.47 (s, 1H), 4.89 (s, 1H), 3.99 (s, 1H),  
10 2.38 (m, 1H), 2.17 (s, 3H), 1.88 (m, 2H), 1.77 (m, 1H), 1.69 (m, 2H), 1.54 (s, 3H), 1.48 (m, 1H), 1.38 (d,  $J = 1.8$ , 3H), 1.20 (d,  $J = 1.2$ , 3H).

## EXAMPLE 2

Preparation of (+)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline  
15 (Compounds **27** and **28**, Structure 3 of Scheme I, where  $\text{R}^8 = \text{R}^9 = \text{R}^{13} = \text{R}^{15} = \text{R}^{18} = \text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $\text{R}^{10} = \text{F}$ ,  $\text{R}^6 = \text{R}^{17} = \text{methyl}$ ,  $\text{R}^{14}/\text{R}^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were obtained through chiral HPLC separation of compound **24** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **27**,  $[\alpha]_{\text{D}}^{22} = +332.3$  and compound **28**,  $[\alpha]_{\text{D}}^{22} = -317.1$  (EtOH).

20

### EXAMPLE 3

Preparation of  $(\pm)$ -(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and  $(\pm)$ -(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **29** and **30**, Structure **3** of Scheme I, where  $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = \text{hydroxy}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and 9-hydroxy-2,2,4-trimethyl-5-methoxy-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline (Compound **31**, Structure **2** of Scheme I, where  $R^8 = R^9 = H$ ,  $R^{10} = \text{hydroxy}$ ,  $R^6 = \text{methyl}$ ).

Compound **29** was isolated as the major isomer:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38 (d,  $J = 8.2$ , 1H), 7.10 (d,  $J = 2.4$ , 1H), 6.86 (d,  $J = 8.5$ , 1H), 6.82 (dt,  $J = 8.6$ , 3.1, 1H), 6.62 (dd,  $J = 8.5$ , 2.7, 1H), 6.60 (d,  $J = 8.2$ , 1H), 5.67 (s, 1H), 5.50 (s, 1H), 5.48 (d,  $J = 12.2$ , 1H), 3.96 (s, 1H), 2.42 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.77 (m, 1H), 1.66 (s, 3H), 1.64 (m, 1H), 1.38 (s, 3H), 1.28 (m, 1H), 1.20 (m, 1H), 1.13 (s, 3H), 1.02 (m, 1H).

Compound **30** was isolated as a minor isomer:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38 (d,  $J = 8.8$ , 1H), 7.18 (d,  $J = 3.7$ , 1H), 7.10 (d,  $J = 3.7$ , 1H), 6.81 (d,  $J = 7.9$ ,

1H), 6.62 (m, 1H), 5.59 (d,  $J = 10.2$ , 1H), 5.47 (s, 1H), 4.90 (s, 1H), 4.45 (s, 1H), 3.96 (s, 1H), 2.40 (m, 1H), 2.17 (s, 3H), 1.88 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.60 (s, 3H), 1.38 (s, 3H), 1.30 (m, 2H), 1.20 (s, 3H), 0.90 (m, 1H).

#### EXAMPLE 4

5        Preparation of (+)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **32** and **33**, Structure **3** of Scheme I, where  $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = \text{hydroxy}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

10        These compounds were obtained through chiral HPLC separation of compound **29** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **32**,  $[\alpha]^{22}_D = +201.6$  and compound **33**,  $[\alpha]^{22}_D = -207.7$  (EtOH).

#### EXAMPLE 5

15        Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, ( $\pm$ )-(5*l*,1'*u*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **34** and **35**, Structure **3** of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ ) and ( $\pm$ )-5-(3-methylenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **87**, Structure **3** of Scheme I,

20

where  $R^9 = R^{13} = R^{14} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^{16}/R^{17} = \text{methylidene}$ ,  $n = 1$ )

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-dimethylphenylsilyl-3-methyl-1-cyclohexene  
5 (Structure 6 of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5-methoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound 36, Structure 5 of Scheme I, where  $R^8 = R^{10} = \text{fluorine}$ ,  $R^9 = H$ ,  $R^6 = \text{methyl}$ ).

Compound 34 was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
10 7.36 (d,  $J = 8.2$ , 1H), 7.29 (dt,  $J = 9.4$ , 1.8, 1H), 6.70 (td,  $J = 9.5$ , 3.0, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.64 (d,  $J = 9.5$ , 1H), 5.63 (s, 1H), 5.51 (s, 1H), 4.04 (s, 1H), 2.38 (m, 1H), 2.24 (s, 3H), 1.88 (m, 1H), 1.77 (m, 1H), 1.69 (m, 1H), 1.65 (s, 3H), 1.39 (s, 3H), 1.30 (m, 1H), 1.25 (m, 1H), 1.14 (s, 3H), 1.10 (m, 1H).

Compound 35 was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
15 7.35 (d,  $J = 8.2$ , 1H), 7.10 (dt,  $J = 9.8$ , 2.4, 1H), 6.70 (td,  $J = 10.8$ , 3.0, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.74 (d,  $J = 10.4$ , 1H), 5.48 (s, 1H), 4.87 (s, 1H), 4.03 (s, 1H), 2.37 (m, 1H), 2.17 (s, 3H), 1.90 (m, 1H), 1.78 (m, 1H), 1.72 (m, 2H), 1.54 (s, 3H), 1.52 (m, 1H), 1.38 (s, 3H), 1.20 (d,  $J = 1.21$ , 3H).

Compound 87 was isolated as a 1.6:1 mixture of two diastereomers:  $^1\text{H}$   
20 NMR (500 MHz,  $\text{CDCl}_3$ ) 7.36 (d,  $J = 8.2$ , 1H), 7.34 (d,  $J = 8.2$ , 1H), 7.14-7.08 (m,



2H), 6.73-6.67 (m, 2H), 6.60 (d,  $J = 11.3$ , 1H), 6.58 (d,  $J = 8.2$ , 1H), 6.10 (d,  $J = 10.1$ , 1H), 5.72 (d,  $J = 10.1$ , 1H), 5.64 (d,  $J = 9.2$ , 1H), 5.62 (s, 1H), 5.51 (s, 1H), 5.42 (s, 1H), 5.39-5.37 (m, 1H), 5.31-5.29 (m, 1H), 4.08-4.02 (m, 1H), 4.01-3.99 (m, 1H), 2.33-2.30 (m, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 2.20-2.00 (m, 4H), 1.99-1.86 (m, 2H), 1.84-1.78 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H), 1.32-1.22 (m, 4H), 1.14 (s, 3H), 1.13 (s, 3H), 0.98-0.92 (m, 2H).

#### EXAMPLE 6

Preparation of (+)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **37** and **38**, Structure **3** of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were obtained through chiral HPLC separation of compound **34** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **37**,  $[\alpha]_D^{22} = +342.4$  and compound **38**,  $[\alpha]_D^{22} = -340.0$  (EtOH).

#### EXAMPLE 7

Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **39**, Structure **3** of Scheme I,

where  $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = \text{methoxy}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

This compound was prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene

5 (Structure 6 of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and 5,9-dimethoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 40, Structure 2 of Scheme I, where  $R^8 = R^9 = H$ ,  $R^{10} = \text{methoxy}$ ,  $R^6 = \text{methyl}$ ) as a yellow solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.43 (d,  $J = 7.9$ , 1H), 7.16 (s, 1H), 6.92 (d,  $J = 8.9$ , 1H), 6.72 (m, 1H), 6.62 (m, 1H), 5.59 (s, 1H), 5.49 (s, 1H),

10 5.48 (d,  $J = 9.8$ , 1H), 3.96 (s, 1H), 3.82 (s, 3H), 2.41 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H), 1.26 (m, 1H), 1.20 (m, 1H), 1.13 (s, 3H), 1.04 (m, 1H).

### EXAMPLE 8

Preparation of ( $\pm$ )-(5*l,l'*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-

15 dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline and ( $\pm$ )-(5*l,l'*)-5-(3-methyl-2-  
cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline  
(Compounds 41 and 42, Structure 3 of Scheme I, where  $R^6 = R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = \text{fluorine}$ ,  $R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were prepared in a similar fashion as that described in

20 Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure 6 of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n$

=1) and 9-fluoro-1,2-dihydro-2,2-dimethyl-5-methoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound 43, Structure 5 of Scheme I, where  $R^{10}$  = fluorine,  $R^6 = R^8 = R^9 = H$ ).

Compound 41 was isolated as a major product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.38 (d,  $J = 8.5$ , 1H), 7.28 (dd,  $J = 9.8$ , 3.1, 1H), 6.89 (dd,  $J = 8.5$ , 4.9, 1H), 6.79 (dt,  $J = 8.6$ , 2.8, 1H), 6.48 (d,  $J = 8.5$ , 1H), 6.43 (d,  $J = 10.1$ , 1H), 5.62 (s, 1H), 5.58 (d,  $J = 10.1$ , 1H), 5.10 (d,  $J = 9.2$ , 1H), 3.86 (s, 1H), 2.44 (m, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.56 (s, 3H), 1.35 (s, 3H), 1.34 (m, 2H), 1.31 (s, 3H), 1.27 (m, 1H).

Compound 42 was isolated as a minor product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.31 (d,  $J = 8.5$ , 1H), 7.28 (dd,  $J = 8.9$ , 2.1, 1H), 6.87 (dd,  $J = 9.2$ , 5.2, 1H), 6.80 (dt,  $J = 8.2$ , 3.1, 1H), 6.49 (d,  $J = 8.2$ , 1H), 6.36 (d,  $J = 10.1$ , 1H), 5.55 (d,  $J = 10.4$ , 1H), 5.10 (d,  $J = 10.1$ , 1H), 4.88 (s, 1H), 3.88 (s, 1H), 2.44 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.60 (m, 2H), 1.56 (s, 3H), 1.52 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H).

### EXAMPLE 9

15 Preparation of  $(\pm)$ -(5*l*, 1'*l*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and  $(\pm)$ -(5*l*, 1'*u*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds 44 and 45, Structure 3 of Scheme I, where  $R^8 = R^9 = R^{13} = R^{15} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = F$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 0$ )

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methylcyclopentene (Compound 46, Structure 6 of Scheme I, where  $R^{17}$  = methyl,  $R^{15} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 0$ ) and compound 26 (Structure 2 of Scheme I, where  $R^8 = R^9 = H$ ,  $R^{10} =$   
5 fluorine,  $R^6$  = methyl).

Compound 44 was isolated as a major product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.38 (d,  $J = 8.5$ , 1H), 7.29 (dd,  $J = 10.4$ , 2.8, 1H), 6.86 (dd,  $J = 8.9$ , 5.2, 1H), 6.79 (dt,  $J = 8.2$ , 3.1, 1H), 6.60 (d,  $J = 8.2$ , 1H), 5.61 (d,  $J = 8.8$ , 1H), 5.52 (s, 1H), 5.34 (s, 1H), 3.99 (s, 1H), 3.00 (m, 1H), 2.24 (s, 3H), 2.29 (m, 1H), 1.63 (m, 2H), 1.55 (s,  
10 3H), 1.38 (s, 3H), 1.14 (s, 3H), 1.06 (m, 1H).

Compound 45 was isolated as a minor product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.38 (d,  $J = 8.2$ , 1H), 7.29 (dd,  $J = 8.8$ , 1.8, 1H), 6.85 (dd,  $J = 8.6$ , 5.2, 1H), 6.81 (dt,  $J = 8.2$ , 3.1, 1H), 6.60 (d,  $J = 8.2$ , 1H), 5.55 (d,  $J = 10.4$ , 1H), 5.47 (s, 1H), 4.81 (s, 1H), 3.99 (s, 1H), 2.96 (m, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 2.14 (s, 3H), 2.09 (m,  
15 1H), 1.91 (m, 1H), 1.55 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H).

### **EXAMPLE 10**

Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and ( $\pm$ )-(5*l*,1'*u*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds 47 and 48, Structure 3 of Scheme I, where  $R^8 = R^9 = R^{13} =$   
20

$R^{15} = R^{18} = R^{21} = H$ ,  $R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = R^{19} = R^{20} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  
 $n = 1$ )

These compounds were prepared in a similar fashion as that described in  
Example 1 general procedure from 3-(dimethylphenylsilyl)-3,5,5-

5 trimethylcyclohexene (Compound **49**, Structure **6** of Scheme I, where  $R^{17} = R^{19} =$   
 $R^{20} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{21} = H$ ,  $n = 1$ ) and compound **26** (Structure **2** of Scheme  
I, where  $R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^8 = R^9 = H$ ).

Compound **47** was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
7.39 (d,  $J = 8.2$ , 1H), 7.30 (dd,  $J = 9.8$ , 3.1, 1H), 6.91 (dd,  $J = 8.9$ , 4.9, 1H), 6.82 (dt,  
10  $J = 8.6$ , 3.1, 1H), 6.62 (d,  $J = 8.2$ , 1H), 5.64 (s, 1H), 5.52 (d,  $J = 9.5$ , 1H), 5.51 (d,  $J$   
 $= 1.2$ , 1H), 4.01 (s, 1H), 2.43 (m, 1H), 2.22 (d,  $J = 1.2$ , 3H), 1.77 (d,  $J = 17.1$ , 1H),  
1.65 (s, 3H), 1.48 (d,  $J = 17.4$ , 1H), 1.38 (s, 3H), 1.12 (s, 3H), 0.88 (t,  $J = 12.2$ , 1H),  
0.81 (s, 3H), 0.77 (m, 1H), 0.58 (s, 3H).

Compound **48** was isolated as a minor isomer:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
15 7.38 (d,  $J = 8.2$ , 1H), 7.28 (dd,  $J = 10.1$ , 2.7, 1H), 6.87 (dd,  $J = 8.9$ , 5.2, 1H), 6.82  
(dt,  $J = 7.9$ , 2.8, 1H), 6.62 (d,  $J = 8.2$ , 1H), 5.56 (d,  $J = 10.1$ , 1H), 5.50 (s, 1H), 4.94  
(s, 1H), 3.99 (s, 1H), 2.42 (m, 1H), 2.17 (s, 3H), 1.83 (s, 1H), 1.56 (m, 4H), 1.38 (s,  
3H), 1.22 (s, 3H), 0.97 (s, 3H), 0.58 (s, 3H).

**EXAMPLE 11**

Preparation of  $(\pm)$ -(5*l,l'*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline,  $(\pm)$ -(5*l,l'*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **50**, **51**, Structure 3 of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 0$ ) and  $(\pm)$ -5-(3-methyl-3-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **52**, Structure 3 of Scheme I, where  $R^9 = R^{13} = R^{14} = R^{15} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{16}/R^{19} = \text{a bond}$ ,  $n = 0$ )

10        These compounds were prepared in a similar fashion as that described in Example 1 general procedure from compound **46** (Structure 6 of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 0$ ) and compound **36** (Structure 2 of Scheme I, where  $R^9 = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ).

Compound **50** was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
15    7.35 (d,  $J = 8.2$ , 1H), 7.08 (d,  $J = 9.5$ , 1H), 6.68 (dt,  $J = 9.6$ , 2.8, 1H), 6.60 (d,  $J = 8.2$ , 1H), 5.73 (d,  $J = 8.5$ , 1H), 5.53 (s, 1H), 5.32 (s, 1H), 4.04 (s, 1H), 2.98 (m, 1H), 2.30 (m, 1H), 2.24 (s, 3H), 2.12 (m, 1H), 1.66 (s, 3H), 1.65 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H), 0.88 (m, 1H).

Compound **51** was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
20    7.35 (d,  $J = 8.5$ , 1H), 7.09 (d,  $J = 7.9$ , 1H), 6.85 (t, 8.5, 1H), 6.60 (d,  $J = 8.2$ , 1H), 5.68 (d,  $J = 10.4$ , 1H), 5.48 (s, 1H), 4.79 (s, 1H), 3.99 (s, 1H), 2.95 (m, 1H), 2.36 (m,

1H), 2.18 (m, 1H), 2.14 (s, 3H), 1.94 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H), 0.88 (m, 1H).

Compound **52** was isolated as minor products: (*syn:anti* ratio of 2.2:1) <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.33 (d, *J* = 8.6, 1H), 7.10 (dt, *J* = 9.8, 2.8, 1H), 6.69 (td, *J* = 9.5, 2.7, 1H), 6.61 (d, *J* = 8.2, 1H), 5.93 (d, *J* = 8.9, 1H), 5.53 (s, 1H), 5.41 (s, 1H), 4.03 (s, 1H), 2.88 (m, 1H), 2.23 (d, *J* = 0.6, 3H), 2.04 (m, 1H), 1.66 (s, 3H), 1.52 (m, 1H), 1.56 (m, 1H), 1.38 (s, 3H), 1.15 (s, 3H), 0.88 (m, 1H).

#### **EXAMPLE 12**

Preparation of (±)-5-(2-cyclopenta-1,3-dienyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **53**, Structure **3** of Scheme I, where R<sup>8</sup> = R<sup>9</sup> = R<sup>15</sup> = R<sup>17</sup> = R<sup>20</sup> = H, R<sup>10</sup> = fluorine, R<sup>6</sup> = methyl, R<sup>13</sup>/R<sup>14</sup> = a bond, R<sup>19</sup>/R<sup>21</sup> a bond, n = 0)

This compound was prepared in a similar fashion as that described in Example 1 general procedure from 5-(dimethylphenylsilyl)-1,3-cyclopentadiene (Compound **54**, Structure **6** of Scheme I, where R<sup>15</sup> = R<sup>17</sup> = R<sup>20</sup> = H, R<sup>19</sup>/R<sup>21</sup> = a bond, n = 0) and compound **26** (Structure **2** of Scheme I, where R<sup>10</sup> = fluorine, R<sup>6</sup> = methyl, R<sup>8</sup> = R<sup>9</sup> = H) as a yellow solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.37 (d, *J* = 8.2, 1H), 7.23 (dd, *J* = 9.5, 2.8, 1H), 6.79 (dd, *J* = 8.6, 4.9, 1H), 6.74 (td, *J* = 8.4, 2.8, 1H), 6.64 (d, *J* = 8.2, 1H), 6.61 (s, 1H), 6.33 (dd, *J* = 5.2, 1.2, 1H), 6.22 (dt, *J* = 5.2, 1.8, 1H), 5.94 (t, *J* = 1.4, 1H), 5.48 (s, 1H), 3.94 (s, 1H), 3.08 (dd, *J* = 23.8, 1.5, 1H), 2.95 (dd, *J* = 23.8, 1.5, 1H), 2.11 (d, *J* = 1.5, 3H), 1.28 (s, 3H), 1.25 (s, 3H).

**EXAMPLE 13**

Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and ( $\pm$ )-(5*l*,1'*u*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline  
5 (Compounds 55 and 56, Structure 3 of Scheme I, where  $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^{17} = \text{ethyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-3-ethylcyclohexene  
10 (Compound 57, Structure 6 of Scheme I, where  $R^{17} = \text{ethyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and compound 26 (Structure 2 of Scheme I, where  $R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^8 = R^9 = H$ ).

Compound 55 was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
7.38 (d,  $J = 8.2$ , 1H), 7.29 (dd,  $J = 9.8$ , 3.1, 1H), 6.90 (dd,  $J = 8.9$ , 4.9, 1H), 6.81 (dt,  
15  $J = 8.2$ , 2.8, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.59 (s, 1H), 5.56 (d,  $J = 9.5$ , 1H), 5.50 (d,  $J = 0.9$ , 1H), 4.00 (s, 1H), 2.40 (m, 1H), 2.24 (d,  $J = 0.9$ , 3H), 1.93 (q,  $J = 6.7$ , 2H), 1.88 (m, 1H), 1.80 (m, 1H), 1.67 (m, 1H), 1.38 (s, 3H), 1.27 (m, 1H), 1.22 (m, 1H), 1.14 (s, 3H), 0.98 (m, 1H), 0.95 (t,  $J = 7.6$ , 3H).

Compound 56 was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
20 7.38 (d,  $J = 7.9$ , 1H), 7.29 (dd,  $J = 9.8$ , 3.1, 1H), 6.86 (m, 1H), 6.82 (m, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.59 (d,  $J = 10.7$ , 1H), 5.46 (s, 1H), 4.92 (s, 1H), 3.98 (s, 1H), 2.40 (m,



1H), 2.18 (s, 3H), 1.98 (m, 1H), 1.85 (q,  $J = 7.9$ , 2H), 1.70 (m, 3H), 1.46 (m, 1H),  
1.38 (s, 3H), 1.20 (s, 3H), 0.98 (m, 1H), 0.94 (t,  $J = 7.6$ , 3H).

#### **EXAMPLE 14**

##### **Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-**

- 5 **dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and ( $\pm$ )-(5*l*,1'*u*)-5-(3-methyl-**  
**2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline**  
**(Compounds 58 and 59, Structure 3 of Scheme I, where  $R^9 = R^{10} = R^{13} = R^{15} = R^{18} =$**   
 **$R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )**

- These compounds were prepared in a similar fashion as that described in
- 10 Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene  
(Structure 6 of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n =$   
1) and 7-fluoro-1,2-dihydro-2,2,4-trimethyl-5-methoxy-5*H*-chromeno[3,4-  
*f*]quinoline (Compound 60, Structure 2 of Scheme I, where  $R^8 = \text{fluorine}$ ,  $R^6 =$   
methyl,  $R^9 = R^{10} = H$ ).

- 15 Compound 58 was isolated as a major product:  $^1\text{H}$  NMR (500 MHz, acetone-  
*d*<sub>6</sub>) 7.54 (d,  $J = 8.2$ , 1H), 7.50 (d,  $J = 7.6$ , 1H), 6.95 (m, 2H), 6.75 (d,  $J = 8.2$ , 1H),  
5.64 (s, 1H), 5.63 (s, 1H), 5.62 (d,  $J = 9.5$ , 1H), 5.54 (s, 1H), 2.36 (m, 1H), 2.23 (s,  
3H), 1.90 (m, 1H), 1.78 (m, 1H), 1.70 (m, 1H), 1.62 (s, 3H), 1.37 (s, 3H), 1.29 (m,  
2H), 1.13 (s, 3H).

Compound **59** was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz, acetone-  
 $d_6$ ) 7.53 (d,  $J = 8.5$ , 1H), 7.50 (d,  $J = 6.7$ , 1H), 6.96 (m, 2H), 6.76 (d,  $J = 8.2$ , 1H),  
5.73 (d,  $J = 10.4$ , 1H), 5.64 (s, 1H), 5.51 (d,  $J = 1.2$ , 1H), 4.96 (m, 1H), 2.35 (m, 1H),  
2.18 (s, 3H), 1.90 (m, 1H), 1.80 (m, 1H), 1.73 (m, 1H), 1.58 (s, 3H), 1.48 (m, 1H),  
5 1.37 (s, 3H), 1.28 (m, 1H), 1.21 (s, 3H).

### EXAMPLE 15

Preparation of  $(\pm)$ -(5*l,l'*)-5-(3-ethyl-2-cyclohexenyl)-7,9-difluoro-1,2-  
dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **61**, Structure **3** of  
Scheme I, where  $\text{R}^9 = \text{R}^{13} = \text{R}^{15} = \text{R}^{18} = \text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $\text{R}^8 = \text{R}^{10} = \text{fluorine}$ ,  $\text{R}^6 =$   
10 methyl,  $\text{R}^{17} = \text{ethyl}$ ,  $\text{R}^{14}/\text{R}^{16} = \text{a bond}$ ,  $n = 1$ ),  $(\pm)$ -(5*l,l'*)-5-(3-ethylidenecyclohexyl)-7,9-  
difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **62**,  
Structure **3** of Scheme I, where  $\text{R}^9 = \text{R}^{13} = \text{R}^{14} = \text{R}^{15} = \text{R}^{18} = \text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $\text{R}^8 = \text{R}^{10}$   
= fluorine,  $\text{R}^6 = \text{methyl}$ ,  $\text{R}^{16}/\text{R}^{17} = \text{ethylidene}$ ,  $n = 1$ ) and  $(\pm)$ -(5*l,l'*)-5-(3-  
ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-  
15 *f*]quinoline (Compound **88**, Structure **3** of Scheme I, where  $\text{R}^9 = \text{R}^{13} = \text{R}^{14} = \text{R}^{15} = \text{R}^{18} =$   
 $\text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $\text{R}^8 = \text{R}^{10} = \text{fluorine}$ ,  $\text{R}^6 = \text{methyl}$ ,  $\text{R}^{16}/\text{R}^{17} = \text{ethylidene}$ ,  $n = 1$ )

These compounds were prepared in a similar fashion as that described in  
Example 1 general procedure from compound **57** (Structure **6** of Scheme I, where  
 $\text{R}^{17} = \text{ethyl}$ ,  $\text{R}^{15} = \text{R}^{18} = \text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $n = 1$ ) and compound **36** (Structure **5** of  
20 Scheme II, where  $\text{R}^8 = \text{R}^{10} = \text{fluorine}$ ,  $\text{R}^6 = \text{methyl}$ ,  $\text{R}^9 = \text{H}$ ).

Compound **61** was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ ) 7.54 (d,  $J = 8.2$ , 1H), 7.31 (dt,  $J = 8.9$ , 1.8, 1H), 6.83 (td, 9.4, 3.0, 1H), 6.76 (d,  $J = 8.2$ , 1H), 5.72 (m, 2H), 5.55 (d,  $J = 4.9$ , 1H), 5.53 (s, 1H), 2.80 (s, 3H), 2.36 (m, 1H), 2.22 (s, 3H), 1.90 (q,  $J = 7.6$ , 2H), 1.82 (m, 1H), 1.72 (m, 1H), 1.30 (m, 1H), 1.37 (s, 3H), 1.14 (s, 3H), 0.90 (t,  $J = 7.6$ , 3H).

Compound **62** was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ ) 7.51 (d,  $J = 8.2$ , 1H), 7.30 (dt,  $J = 10.1$ , 2.8, 1H), 6.83 (td, 9.6, 2.8, 1H), 6.75 (d,  $J = 8.6$ , 1H), 5.87 (d,  $J = 10.1$ , 1H), 5.71 (s, 1H), 5.57 (d,  $J = 1.5$ , 1H), 5.03 (m, 1H), 2.84 (s, 3H), 2.39 (m, 1H), 2.16 (m, 1H), 2.22 (m, 1H), 1.90 (m, 2H), 1.82 (m, 1H), 1.70 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H), 0.83 (d,  $J = 7.3$ , 3H).

Compound **88** was isolated as a 1:1 mixture of two E/Z-isomers:  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ ) 7.50 (d,  $J = 8.5$ , 1H), 7.49 (d,  $J = 8.5$ , 1H), 7.34-7.24 (m, 2H), 6.90-6.80 (m, 2H), 6.64 (d,  $J = 8.5$ , 1H), 6.61 (d,  $J = 8.5$ , 1H), 5.86 (d,  $J = 7.9$ , 1H), 5.80 (d,  $J = 7.9$ , 1H), 5.49 (s, 1H), 5.36 (s, 1H), 5.34 (s, 1H), 5.22 (s, 1H), 5.16 (s, 1H), 4.79 (s, 1H), 2.44-2.38 (m, 1H), 2.34-2.28 (m, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.90-1.74 (m, 6H), 1.68-1.58 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.36-1.22 (m, 8H), 1.22 (s, 3H), 1.18 (s, 3H), 0.92-0.84 (m, 6H).

#### **EXAMPLE 16**

Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3-methyl-3-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **63**, Structure 3 of

Scheme I, where  $R^9 = R^{13} = R^{14} = R^{15} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{16}/R^{18} = \text{a bond}$ ,  $n = 1$ )

This compound was isolated as a minor product after treatment of compound  
34 (Structure 3 of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 =$   
5  $R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ ) with acid:  $^1H$  NMR (500  
MHz,  $CDCl_3$ ) 7.33 (d,  $J = 8.5$ , 1H), 7.10 (d,  $J = 10.1$ , 1H), 6.70 (td,  $J = 10.4$ , 2.4,  
1H), 6.60 (d,  $J = 8.5$ , 1H), 6.01 (d,  $J = 7.9$ , 1H), 5.51 (s, 1H), 5.47 (s, 1H), 4.04 (s,  
1H), 2.41 (m, 1H), 2.24 (s, 3H), 1.95 (m, 2H), 1.86 (s, 3H), 1.52 (m, 1H), 1.38 (s,  
3H), 1.18 (m, 1H), 1.14 (s, 3H), 1.12 (m, 1H), 0.97 (m, 1H).

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#### EXAMPLE 17

Preparation of ( $\pm$ )-(5*l*,1'*l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-  
dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and ( $\pm$ )-(5*l*,1'*u*)-5-  
(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-  
chromeno[3,4-*f*]quinoline (Compounds 64 and 65, Structure 3 of Scheme I, where  
15  $R^8 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^9 = \text{methoxy}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{10} =$   
fluorine,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

These compounds were prepared in a similar fashion as that described in  
Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene  
(Structure 6 of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n =$   
20 1) and 9-fluoro-1,2-dihydro-5,8-dimethoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-

*f*]quinoline (Compound 66, Structure 2 of Scheme I, where  $R^8 = H$ ,  $R^6 = \text{methyl}$ ,  $R^9 = \text{methoxy}$ ,  $R^{10} = \text{fluorine}$ ).

Compound 64 was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ ) 7.44 (d,  $J=12.5$ , 1H), 7.42 (d,  $J=8.2$ , 1H), 6.73 (d,  $J=6.6$ , 1H), 6.71  
5 (d,  $J=7.2$ , 1H), 5.68 (s, 1H), 5.52 (m, 2H), 5.48 (s, 1H), 3.90 (s, 3H), 2.40 (m, 1H),  
2.20 (s, 3H), 2.08 (m, 1H), 1.96 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.63 (s, 3H),  
1.36 (s, 3H), 1.26 (m, 2H), 1.12 (s, 3H).

Compound 65 was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ ) 7.44 (d,  $J=12.5$ , 1H), 7.42 (d,  $J=8.2$ , 1H), 6.73 (d,  $J=8.2$ , 1H), 6.70  
10 (d,  $J=7.6$ , 1H), 5.63 (s, 1H), 5.48 (s, 1H), 5.46 (d,  $J=12.5$ , 1H), 4.96 (m, 1H), 3.88  
(s, 3H), 2.39 (m, 1H), 2.20 (s, 3H), 1.94 (m, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.57  
(s, 3H), 1.46 (m, 1H), 1.36 (s, 3H), 1.28 (m, 2H), 1.20 (s, 3H).

### **EXAMPLE 18**

Preparation of ( $\pm$ )-(5*l,l'*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-  
15 trimethyl-5*H*-chromeno[3,4-*f*]quinoline, ( $\pm$ )-(5*l,l'*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-  
dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds 67, 68, Structure 3  
of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{17} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 =$   
methyl,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 0$ ) and ( $\pm$ )-5-(1-cyclopentenyl)-7,9-difluoro-1,2-dihydro-  
2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 69, Structure 3 of Scheme I,  
20 where  $R^9 = R^{15} = R^{16} = R^{17} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  
 $R^{13}/R^{14} = \text{a bond}$ ,  $n = 0$ )

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)cyclopentene (Compound 70, Structure 6 of Scheme I, where  $R^{15} = R^{17} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 0$ ) and compound 36 (Structure 2 of Scheme I, where  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^9 = H$ ).

Compound 61 was isolated as a major product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.37 (d,  $J = 8.2$ , 1H), 7.10 (dt,  $J = 9.5$ , 2.7, 1H), 6.71 (td,  $J = 9.5$ , 3.1, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.77 (ddd, 1H), 5.71 (d,  $J = 10.4$ , 1H), 5.48 (d,  $J = 1.2$ , 1H), 5.23 (ddd, 1H), 5.53 (s, 1H), 4.02 (s, 1H), 3.01 (m, 1H), 2.46 (m, 1H), 2.28 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.39 (s, 3H), 1.28 (m, 2H), 1.19 (s, 3H).

Compound 62 was isolated as a minor product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.37 (d,  $J = 8.2$ , 1H), 7.09 (dt,  $J = 9.8$ , 1.8, 1H), 6.69 (td,  $J = 9.6$ , 2.8, 1H), 6.61 (d,  $J = 8.6$ , 1H), 5.78 (m, 1H), 5.77 (s, 1H), 5.75 (s, 1H), 5.74 (m, 1H), 5.53 (s, 1H), 4.05 (s, 1H), 2.93 (m, 1H), 2.38 (m, 1H), 2.24 (d,  $J = 0.9$ , 3H), 1.63 (m, 2H), 1.39 (s, 3H), 1.15 (s, 3H).

Compound 63 was isolated as a minor product:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.31 (d,  $J = 8.6$ , 1H), 7.04 (m, 1H), 6.66 (m, 1H), 6.61 (d,  $J = 8.6$ , 1H), 6.31 (m, 1H), 5.49 (m, 1H), 5.16 (q,  $J = 1.8$ , 1H), 3.96 (s, 1H), 2.52 (m, 1H), 2.35 (m, 1H), 2.18 (s, 3H), 1.85 (m, 1H), 1.78 (m, 1H), 1.29 (d,  $J = 20.8$ , 3H), 1.16 (m, 2H), 1.15 (s, 3H).

**EXAMPLE 19**

Preparation of ( $\pm$ )-(5*l*, 1'*l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 71,

Structure 3 of Scheme I, where  $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,

5  $R^6 = R^{15} = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 0$ )

This compound was prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-2,3-dimethylcyclopentene (Compound 72, Structure 6 of Scheme I, where  $R^{19} = R^{20} = R^{21} = H$ ,  $R^{15} = R^{17} = \text{methyl}$ ,  $n = 0$ ) and compound 36 (Structure 2 of Scheme I, 10 where  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^9 = H$ ) as a yellow solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.32 (d,  $J = 8.2$ , 1H), 7.09 (dt,  $J = 9.8$ , 2.7, 1H), 6.69 (td,  $J = 10.8$ , 2.8, 1H), 6.59 (d,  $J = 7.5$ , 1H), 5.92 (d,  $J = 8.2$ , 1H), 5.53 (s, 1H), 4.01 (s, 1H), 2.86 (m, 1H), 2.29 (m, 1H), 2.22 (s, 3H), 2.00 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.50 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H).

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**EXAMPLE 20**

Preparation of (+)-(5*l*, 1'*l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-(5*l*, 1'*l*)-5-(2,3-

dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-

chromeno[3,4-*f*]quinoline (Compounds 73 and 74, Structure 3 of Scheme I, where

20  $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{15} = R^{17} = \text{methyl}$ ,

$R^{14}/R^{16} = \text{a bond}$ ,  $n = 0$ )

These compounds were obtained through chiral HPLC separation of compound **71** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **73**,  $[\alpha]_D^{22} = +256.7$  and compound **74**,  $[\alpha]_D^{22} = -263.8$  (EtOH).

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### EXAMPLE 21

Preparation of ( $\pm$ )-(5*L*,1'*L*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, ( $\pm$ )-(5*L*,1'*u*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **75** and **76**, Structure **3** of Scheme I, where  $R^9 = R^{15} = R^{16} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^{13}/R^{14} = \text{a bond}$ ,  $n = 1$ ) and ( $\pm$ )-(5*L*,1'*L*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (Compound **77**, Structure **4** of Scheme I, where  $R^4 = R^{17} = H$ ,  $X = O$ )

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These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)cyclohexene (Compound **78**, Structure **6** of Scheme I, where  $R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and compound **36** (Structure **2** of Scheme I, where  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^9 = H$ ).

15

Compound **75** was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.35 (d,  $J = 8.2$ , 1H), 7.08 (td,  $J = 9.8$ , 1.8, 1H), 6.69 (dt,  $J = 9.5$ , 3.0, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.90 (d,  $J = 11.0$ , 1H), 5.76 (m, 1H), 5.68 (d,  $J = 9.5$ , 1H), 5.52 (d,  $J =$

20



1.2, 1H), 4.06 (s, 1H), 2.41 (m, 1H), 2.24 (d,  $J = 1$ , 3H), 1.94 (m, 2H), 1.66 (m, 2H),  
1.39 (s, 3H), 1.28 (m, 1H), 1.25 (m, 1H), 1.14 (s, 3H).

Compound **76** was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
7.35 (d,  $J = 8.2$ , 1H), 7.10 (td,  $J = 9.8$ , 1.8, 1H), 6.70 (dt,  $J = 8.6$ , 2.7, 1H), 6.60 (d,  $J$   
5 = 8.2, 1H), 5.78 (d,  $J = 10.4$ , 1H), 5.68 (m, 1H), 5.48 (s, 1H), 5.12 (d,  $J = 7.9$ , 1H),  
4.04 (s, 1H), 2.41 (m, 1H), 2.20 (s, 3H), 1.98 (m, 2H), 1.78 (m, 2H), 1.38 (s, 3H),  
1.28 (m, 1H), 1.25 (m, 1H), 1.18 (s, 3H).

Compound **77** was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
7.31 (d,  $J = 8.6$ , 1H), 7.08 (m, 1H), 6.68 (m, 1H), 6.43 (d,  $J = 8.2$ , 1H), 5.85 (m,  
10 1H), 5.73 (m, 1H), 5.40 (s, 1H), 5.18 (s, 1H), 4.04 (s, 1H), 2.33 (d,  $J = 11.3$ , 1H),  
2.27 (d,  $J = 12.2$ , 1H), 2.00 (m, 1H), 1.93 (m, 1H), 1.68 (m, 1H), 1.94 (m, 2H), 1.34  
(s, 3H), 1.18 (m, 1H), 1.14 (s, 3H), 0.86 (m, 2H).

## **EXAMPLE 22**

Preparation of  $(\pm)$ -(5*l,l'*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-  
15 dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and  $(\pm)$ -(5*l,l'*)-5-(2-  
methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-  
*f*]quinoline (Compounds **79** and **80**, Structure 3 of Scheme I, where  $\text{R}^8 = \text{R}^9 = \text{R}^{13} =$   
 $\text{R}^{16} = \text{R}^{17} = \text{R}^{18} = \text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $\text{R}^{10} = \text{fluorine}$ ,  $\text{R}^6 = \text{methyl}$ ,  $\text{R}^{14}/\text{R}^{15} =$   
methylidene,  $n = 1$ )

(±)-(5*l,l'*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-(5*l,l'**u*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **81** and **82**, Structure **3** of Scheme I, where  $R^8 = R^9 = R^{13} = R^{16} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^{14}/R^{15} = \text{carbonyl}$ ,  $n = 1$ )

Compounds **81** and **82** were prepared in a similar fashion as that described in Example 1 general procedure from 1-(trimethylsilyloxy)cyclohexene and compound **26** (Structure 2 of Scheme I, where  $R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^8 = R^9 = H$ ).

Compound **81** was isolated as a major product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.36 (d,  $J = 8.6$ , 1H), 7.30 (dd,  $J = 13.4$ , 4.6, 1H), 6.81 (d,  $J = 7.0$ , 1H), 6.80 (d,  $J = 8.2$ , 1H), 6.61 (d,  $J = 8.5$ , 1H), 6.58 (d,  $J = 9.2$ , 1H), 5.49 (s, 1H), 3.99 (s, 1H), 2.84 (m, 1H), 2.45 (m, 1H), 2.28 (s, 3H), 2.24 (m, 1H), 1.99 (m, 1H), 1.68 (m, 2H), 1.40 (m, 2H), 1.37 (s, 3H), 1.11 (s, 3H).

Compound **82** was isolated as a minor product:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.36 (d,  $J = 8.6$ , 1H), 7.30 (dd,  $J = 7.3$ , 1H), 6.81 (d,  $J = 8.8$ , 1H), 6.79 (d,  $J = 7.6$ , 1H), 6.59 (d,  $J = 8.2$ , 1H), 6.44 (d,  $J = 5.8$ , 1H), 5.49 (s, 1H), 3.99 (s, 1H), 2.59 (m, 1H), 2.35 (m, 1H), 2.26 (s, 3H), 2.20 (m, 1H), 1.90 (m, 2H), 1.80 (m, 1H), 1.70 (m, 2H), 1.45 (m, 2H), 1.37 (s, 3H), 1.12 (s, 3H).

The title compounds **79** and **80** were prepared by using a Wittig procedure from compounds **81** and **82**. Data for compound **79**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

7.38 (d,  $J = 8.2$ , 1H), 7.31 (dd,  $J = 7.6, 2.8$ , 1H), 6.78 (m, 1H), 6.80 (d,  $J = 8.2$ , 1H), 6.61 (m, 1H), 6.02 (d,  $J = 10.1$ , 1H), 5.52 (s, 1H), 4.83 (s, 1H), 4.71 (s, 1H), 4.02 (s, 1H), 2.50 (m, 1H), 2.42 (s, 3H), 2.30 (m, 1H), 2.07 (m, 1H), 1.60 m, m1H), 1.45 (m, 2H), 1.39 (s, 3H), 1.30 (m, 1H), 1.18 (m, 1H), 1.12 (s, 3H), 1.08 (m, 1H). Data for  
5 compound **80**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38 (d,  $J = 8.8$ , 1H), 7.34 (m, 1H), 6.78 (m, 1H), 6.86 (m, 1H), 6.54 (d,  $J = 8.9$ , 1H), 6.01 (d,  $J = 9.2$ , 1H), 5.47 (s, 1H), 4.41 (s, 1H), 4.10 (s, 1H), 3.98 (s, 1H), 2.56 (m, 1H), 2.30 (s, 3H), 2.04 (m, 3H), 1.76 (m, 1H), 1.68 (m, 1H), 1.58 (m, 1H), 1.36 (s, 3H), 1.30 (m, 2H), 1.09 (s, 3H).

### **EXAMPLE 23**

10 Preparation of ( $\pm$ )-(*5*l*,1'*l**)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-1,2,2,4-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **83**, Structure **5** of Scheme I)

This compound was prepared by methylation of compound **39** (Structure **3** of Scheme I, where  $\text{R}^8 = \text{R}^9 = \text{R}^{13} = \text{R}^{15} = \text{R}^{18} = \text{R}^{19} = \text{R}^{20} = \text{R}^{21} = \text{H}$ ,  $\text{R}^{10} = \text{methoxy}$ ,  $\text{R}^6 = \text{R}^{17} = \text{methyl}$ ,  $\text{R}^{14}/\text{R}^{16} = \text{a bond}$ ,  $n = 1$ )) as a yellow solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.56 (d,  $J = 8.5$ , 1H), 7.28 (d,  $J = 2.1$ , 1H), 6.92 (d,  $J = 8.9$ , 1H), 6.75 (m, 2H), 5.69 (s, 1H), 5.54 (s, 1H), 5.50 (d,  $J = 9.8$ , 1H), 3.83 (s, 3H), 2.89 (s, 3 H), 2.41 (m, 1H), 2.26 (s, 3H), 1.87 (m, 1H), 1.77 (m, 1H), 1.66 (s, 3H), 1.62 (m, 1H), 1.51 (s, 3H), 1.28 (m, 2H), 1.18 (m, 1H), 0.96 (s, 3H).

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#### **EXAMPLE 24**

Preparation of ( $\pm$ )-5-(2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compounds **84**, Structure **3** of Scheme I, where  $R^8 = R^9 = R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^{10} = F$ ,  $R^6 = \text{methyl}$ ,  $R^{14}/R^{16}$  = a bond,  $n = 1$ )

This compound was prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)cyclohexene (Compound **78**, Structure **6** of Scheme I, where  $R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and compound **26** (Structure **2** of Scheme I, where  $R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^8 = R^9 = H$ ) as a 1:1 mixture of two diastereomers:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38 (d,  $J = 8.2$ , 1H), 7.38 (d,  $J = 8.2$ , 1H), 7.30 (t,  $J = 2.8$ , 1H), 7.28 (t,  $J = 2.8$ , 1H), 6.90-6.85 (m, 2H), 6.85-6.80 (m, 2H), 6.61 (d,  $J = 8.2$ , 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.91 (d,  $J = 10.1$ , 1H), 5.78-5.71 (m, 1H), 5.67 (d,  $J = 10.1$ , 1H), 5.70-5.64 (m, 1H), 5.57 (d,  $J = 9.8$ , 1H), 5.51 (s, 1H), 5.47 (s, 1H), 5.18-5.14 (m, 1H), 4.02-3.98 (m, 2H), 2.46-2.38 (m, 1H), 2.24 (s, 3H), 2.20 (s, 3H), 2.04-1.90 (m, 4H), 1.80-1.70 (m, 3H), 1.68-1.62 (m, 1H), 1.48-1.42 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.32-1.22 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 0.98-0.92 (m, 2H).

#### **EXAMPLE 25**

Preparation of ( $\pm$ )-5-(2,3-dimethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound **85**, Structure **3** of Scheme I, where  $R^9 = R^{13} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{15} = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ )

This compound was prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-2,3-dimethylcyclohexene (Compound **86**, Structure 6 of Scheme I, where  $R^{18}=R^{19}=R^{20}=R^{21}=H$ ,  $R^{15}=R^{17}=\text{methyl}$ ,  $n=1$ ) and Compound **36** (Structure 2 of Scheme I, where  $R^8=R^{10}=\text{fluorine}$ ,  $R^9=H$ ,  $R^6=\text{methyl}$ ) as a yellow solid:  $^1H$  NMR (500 MHz, acetone- $d_6$ ) 7.50 (d,  $J=8.2$ , 1H), 7.30 (dt,  $J=10.1$ , 1.8, 1H), 6.84 (td,  $J=9.8$ , 2.8, 1H), 6.75 (d,  $J=8.2$ , 1H), 6.01 (d,  $J=6.4$ , 1H), 5.72 (s, 1H), 5.55 (d, 1.2, 1H), 2.30 (m, 1H), 2.22 (s, 3H), 2.00-1.8 (m, 3H), 1.59 (s, 3H), 1.50 (s, 3H), 1.46-1.40 (m, 1H), 1.37 (s, 3H), 1.36-1.26 (m, 3H), 1.15 (s, 3H).

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### EXAMPLE 26

Preparation of ( $\pm$ )-(5*L*,1'*L*)-5-(2-cycloheptenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **89**, Structure 3 of Scheme I, where  $R^9=R^{13}=R^{15}=R^{17}=R^{18}=R^{19}=R^{20}=R^{21}=H$ ,  $R^8=R^{10}=\text{fluorine}$ ,  $R^6=\text{methyl}$ ,  $R^{14}/R^{16}=\text{a bond}$ ,  $n=2$ )

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This compound was prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)cycloheptene (Compound **90**, Structure 6 of Scheme I, where  $R^{15}=R^{17}=R^{18}=R^{19}=R^{20}=R^{21}=H$ ,  $n=2$ ) and Compound **36** (Structure 2 of Scheme I, where  $R^8=R^{10}=\text{fluorine}$ ,  $R^9=H$ ,  $R^6=\text{methyl}$ ) as a yellow solid:  $^1H$  NMR (500 MHz,  $CDCl_3$ ) 7.36 (d,  $J=8.6$ , 1H), 7.10 (d,  $J=9.8$ , 1H), 6.68 (ddd,  $J=9.5$ , 2.8, 2.8, 1H), 6.61 (d,  $J=8.2$ , 1H), 6.03 (d,  $J=11.6$ , 1H), 5.84-5.76 (m, 1H), 5.80 (d,  $J=10.1$ , 1H), 5.52 (s, 1H), 4.10 (s, 1H), 2.47

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(m, 1H), 2.24 (s, 3H), 2.12-2.04 (m, 2H), 1.94-1.84 (m, 1H), 1.78-1.84 (m, 1H),  
1.44-1.44 (m, 1H), 1.38 (s, 3H), 1.24-1.18 (m, 2H), 1.11 (s, 3H), 0.98-0.92 (m, 1H).

### **EXAMPLE 27**

Preparation of (±)-(5*l*,1'*l*)- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-  
5 2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-(5*l*,1'*u*)- 5-(2-cyclooctenyl)-  
7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds  
91 and 92, Structure 3 of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} =$   
 $R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 3$ )

These compounds were prepared in a similar fashion as that described in  
10 Example 1 general procedure from 3-(dimethylphenylsilyl)cyclooctene (Compound  
93, Structure 6 of Scheme I, where  $R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n =$   
3) and Compound 36 (Structure 2 of Scheme I, where  $R^8 = R^{10} = \text{fluorine}$ ,  $R^9 = H$ ,  
 $R^6 = \text{methyl}$ ) as a yellow solid: Compound 91  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.36 (d,  
 $J = 8.6$ , 1H), 7.10 (d,  $J = 9.8$ , 1H), 6.68 (ddd,  $J = 9.5$ , 2.8, 2.8, 1H), 6.58 (d,  $J = 8.2$ ,  
15 1H), 5.87 (d,  $J = 9.5$ , 1H), 5.74-5.66 (m, 1H), 5.56 (t,  $J = 10.1$ , 1H), 5.52 (s, 1H),  
4.03 (s, 1H), 2.90-2.80 (m, 1H), 2.26 (s, 3H), 1.88-1.80 (m, 1H), 1.54-1.46 (m, 2H),  
1.40-1.32 (m, 2H), 1.23-1.17 (m, 2H), 1.38 (s, 3H), 1.24-1.18 (m, 2H), 1.19 (s, 3H),  
1.07-0.98 (m, 1H); Compound 92  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.33 (d,  $J = 8.5$ , 1H),  
7.11 (d,  $J = 9.8$ , 1H), 6.71 (ddd,  $J = 9.5$ , 2.8, 2.8, 1H), 6.61 (d,  $J = 8.2$ , 1H), 5.87 (d,  
20  $J = 8.8$ , 1H), 5.54 (s, 1H), 5.54-5.48 (m, 1H), 5.23 (t,  $J = 10.4$ , 1H), 4.01 (s, 1H),  
2.88-2.80 (m, 1H), 2.26 (s, 3H), 1.96-1.88 (m, 1H), 1.84-1.70 (m, 2H), 1.54-1.46 (m,

2H), 1.45-1.38 (m, 1H), 1.38 (s, 3H), 1.36-1.26-1.17 (m, 2H), 1.20-1.00 (m, 2H),  
1.10 (s, 3H).

### **EXAMPLE 28**

Preparation of (±)-(5*l*,1'*l*)- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-  
5 1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 94, Structure  
3 of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} =$   
fluorine,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = -O-$ ,  $n = 1$ ) and (±)-(5*l*,1'*l*)- 5-(3-methyl-2-  
cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro- 2,2-dimethyl-4-methylene-5*H*-  
chromeno[3,4-*f*]quinolin-3-ol (Compound 95, Structure 4 of Scheme I, where  $R^4 =$   
10 hydroxy,  $R^{17} = \text{methyl}$ ,  $X = O$ )

These compounds were prepared by epoxidation of Compound 34 (Structure  
3 of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} =$   
fluorine,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ ) according to a standard  
procedure as yellow solids: Compound 94,  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ ) 7.54 (d,  
15  $J = 8.5$ , 1H), 7.35 (ddd,  $J = 9.2, 1.8, 1.8$ , 1H), 6.89 (ddd,  $J = 9.5, 2.8, 2.8$ , 1H), 6.76  
(d,  $J = 8.5$ , 1H), 6.02 (d,  $J = 10.1$ , 1H), 5.74 (s, 1H), 5.54 (s, 1H), 3.15 (d,  $J = 2.1$ ,  
1H), 2.28 (d,  $J = 0.6$ , 3H), 2.16-2.00 (m, 1H), 1.72-1.66 (m, 2H), 1.37 (s, 3H), 1.40-  
1.28 (m, 1H), 1.28 (s, 3H), 1.11 (s, 3H), 1.08-0.93 (m, 2H), 0.84-0.76 (m, 1H);  
Compound 95,  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ ) 7.48 (d,  $J = 8.5$ , 1H), 7.28 (ddd,  $J =$   
20 9.2, 1.8, 1.8, 1H), 6.83 (ddd,  $J = 9.5, 2.8, 2.8$ , 1H), 6.60 (d,  $J = 8.5$ , 1H), 5.80 (d,  $J =$   
8.8, 1H), 5.70 (d,  $J = 21.4$ , 1H), 5.68 (s, 1H), 5.55 (s, 1H), 5.41 (s, 1H), 4.55 (d,  $J =$

4.9, 1H), 4.18 (dt,  $J = 4.6, 1.2$ , 1H), 2.30-2.22 (m, 1H), 1.90-1.74 (m, 1H), 1.74-1.66 (m, 1H), 1.58 (s, 3H), 1.35 (s, 3H), 1.32-1.24 (m, 4H), 1.08 (s, 3H).

### **EXAMPLE 29**

Preparation of  $(\pm)$ -(5*l, l'*)- 5-(2,3-epoxy-2,3-dimethylcyclopentyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **96**,  
5 Structure 3 of Scheme I, where  $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{15} = R^{17} = \text{methyl}$ ,  $R^{14}/R^{15} = -O-$ ,  $n = 0$ )

This compound was prepared by epoxidation of Compound **71** (Structure **3**  
of Scheme I, where  $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{15} =$   
10  $R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 0$ ) as a solid:  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  
7.49 (d,  $J = 8.5$ , 1H), 7.34 (ddd,  $J = 9.2, 1.8, 1.8$ , 1H), 6.89 (ddd,  $J = 9.5, 2.8, 2.8$ ,  
1H), 6.73 (d,  $J = 8.6$ , 1H), 6.18 (d,  $J = 9.5$ , 1H), 5.68 (s, 1H), 5.53 (s, 1H), 2.35 (dt,  $J$   
= 9.8, 1.8, 1H), 2.28 (d,  $J = 0.6$ , 3H), 1.69 (dd,  $J = 13.7, 8.2$ , 1H), 1.48 (s, 3H), 1.47-  
1.43 (m, 1H), 1.36 (s, 3H), 1.25 (s, 3H), 1.01 (s, 3H), 0.98-0.92 (m, 1H), 0.78-0.72  
15 (m, 1H).

### **EXAMPLE 30**

Preparation of  $(\pm)$ -(5*l, l'*)- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-  
1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **97**, Structure  
3 of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} =$   
20 fluorine,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = -O-$ ,  $n = 1$ )



This compound was prepared by epoxidation of Compound **35** (Structure **3** of Scheme I, where  $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $R^8 = R^{10} = \text{fluorine}$ ,  $R^6 = R^{17} = \text{methyl}$ ,  $R^{14}/R^{16} = \text{a bond}$ ,  $n = 1$ ) according to a standard procedure as yellow solids: Compound **97**,  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ ) 7.57 (d,  $J = 8.5$ , 1H),  
 5 7.35 (ddd,  $J = 9.2, 1.8, 1.8$ , 1H), 6.88 (ddd,  $J = 9.5, 2.8, 2.8$ , 1H), 6.80 (d,  $J = 8.5$ , 1H), 5.94 (d,  $J = 10.4$ , 1H), 5.77 (s, 1H), 5.61 (s, 1H), 2.65 (s, 1H), 2.27 (d,  $J = 0.9$ , 3H), 2.12-2.06 (m, 1H), 1.86-1.80 (m, 1H), 1.76-1.68 (m, 1H), 1.66-1.58 (m, 1H), 1.46-1.40 (m, 1H), 1.37 (s, 3H), 1.36-1.26 (m, 2H), 1.21 (s, 3H), 1.11 (s, 3H).

### EXAMPLE 31

10 Preparation of ( $\pm$ )-(5*l*,1'*l*)- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinolin-4-one (Compound **98**, Structure **4** of Scheme I, where  $R^4 = H$ ,  $R^{17} = \text{methyl}$ ,  $X = O$ )

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene  
 15 (Structure **6** of Scheme I, where  $R^{17} = \text{methyl}$ ,  $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$ ,  $n = 1$ ) and 7,9-difluoro-1,2,3,4-tetrahydro-5-methoxy-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinolin-4-one (Compound **99**).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ), 7.55 (d,  $J = 8.9$ , 1H), 7.02-6.95 (m, 1H), 6.70-6.64 (m, 1H), 6.66 (d,  $J = 8.6$ , 1H), 6.42 (d,  $J = 5.8$ , 1H), 5.26 (s, 1H), 4.42 (s, 1H), 2.67 (d,  $J = 15.2$ , 1H), 2.56 (d,  $J = 15.0$ , 1H), 2.48  
 20 (m, 1H), 1.94-1.80 (m, 2H), 1.78-1.66 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.42-1.36 (m, 1H), 1.29-1.25 (m, 1H).

### **EXAMPLE 32**

The in vitro activity of selected hPR modulator compounds of the present invention were evaluated utilizing the cotransfection assay, and in standard receptor competitive binding assays, according to the following illustrative Examples.

#### **5   Cotransfection assay**

The function and detailed preparation procedure of the cotransfection assays have been described previously (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga *Cymopolia Barbata*. *Mol. Pharm.* **1995**, *47*, 630-635). Briefly, the cotransfection assays were carried out in

10   CV-1 cells (African green monkey kidney fibroblasts), which were transiently transfected, by the standard calcium phosphate coprecipitation procedure (Berger, T. S. *et al.*, Interaction of Glucocorticoid Analogues with the Human Glucocorticoid Receptor. *J. Steroid Biochem. Mol. Bio.* **1992**, *41*, 733-738) with the Plasmid containing receptor, MTV-LUC reporter, pRS- $\beta$ -Gal, and filler DNA (Rous sarcoma

15   virus chloramphenicol acetyltransferase). The agonist activity was determined by examining the LUC expression (normalized response) and the efficacy readout was a relative value to the maximal LUC expression produced by progesterone. All the cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

**Receptor Binding Assays**

The preparation of receptor binding assays for hPR-A was described in literature (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga *Cymopolia Barbata*. *Mol. Pharm.* **1995**, 47, 630-  
5 635.)

The agonist, antagonist and binding activity assay results of selected progesterone receptor modulator compounds of the present invention and the standard reference compounds on PR are shown in Table 1 below. Efficacy is reported as the percent maximal response observed for each compound relative to  
10 the reference agonist and antagonist compounds indicated above. Also reported in Table 1 for each compound is its antagonist potency or  $IC_{50}$  (which is the concentration (nM), required to reduce the maximal response by 50%), and its agonist potency or  $EC_{50}$  (nM), which is the effective concentration that produced 50% of the maximum response.

**Table 1: Agonist, antagonist and binding activity of progesterone receptor modulator compounds of present invention and the reference agonist compound, progesterone (Prog), and reference antagonist compound, RU486 and ZK299.**

5

Cmpd No.	PR Agonist CV-1 Cells		PR Antagonist CV-1 Cells		PR Binding
	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K <sub>i</sub> (nM)
Prog	100	2.9	na	na	3.5
RU486	na	na	96	0.18	0.58
ZK299	na	na	99	1.6	18
24	168	3.6	na	na	6.4
25	86	9.7	na	na	6.3
27	68	43	na	na	241
28	171	0.9	na	na	2.0
34	164	0.5	na	na	3.7
35	100	5.4	na	na	14
37	na	na	50	113	>1000
38	166	0.6	na	na	1.9
41	122	10	na	na	11
42	27	38	na	na	143
44	123	6.7	na	na	7.7
45	94	9.1	na	na	17
64	na	na	80	1900	485
65	na	na	59	650	329
71	139	3.4	na	na	3.9

na = not active (*i.e.* efficacy of <20 and potency of >10,000)

### **EXAMPLE 33**

The in vivo activity of selected hPR modulator compounds of the present invention were evaluated utilizing the McPhail assay, according to the following illustrative Examples. The Clauberg or McPhail assay is a classic assay utilizing rabbits to measure progestational activity. The reason rabbit is used is because the results observed in rabbit have proved to be a good indicator and predictor of

activity in the human. In this assay, immature rabbits are treated initially with estradiol, which induces growth in the uterus. This is followed by treatment with a progestin, which causes a large change in the glandular content of the uterus. It is this change in the glandular component, which is a measure of the progestational activity of a progestin. The measurement of these glandular changes are carried out histologically using stained sections of the uterus. The assay results of the new 5-cycloalkenyl compounds are tabulated in Table 2. The in vivo potency of the progestins is presented as the minimum active dose (MAD) in mg/kg.

10 **Table 2: The potency (MAD in mg/kg) of selected 5-cycloalkenyl compounds of present invention in the McPhail assay.**

Compd #	MAD (mg/kg)	EC <sub>50</sub> (nM)	K <sub>i</sub> (nM)
24	0.25	3.6	6.4
34	0.25	0.5	3.7
38	0.10	0.6	1.9
71	0.25	3.4	3.9

### **Pharmacological and Other Applications**

The following Example provides illustrative pharmaceutical composition formulations:

#### **EXAMPLE 34**

Hard gelatin capsules are prepared using the following ingredients:

	<b>Quantity (mg/capsule)</b>
COMPOUND 24	10
Starch, dried	100
Magnesium stearate	<u>10</u>
Total	120 mg

The above ingredients are mixed and filled into hard gelatin capsules in 120 mg quantities.

A tablet is prepared using the ingredients below:

	<b>Quantity (mg/tablet)</b>
COMPOUND 24	10
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	<u>10</u>
Total	230 mg

5

The components are blended and compressed to form tablets each weighing 230 mg.

Tablets, each containing 10 mg of active ingredient, are made as follows:

	<b>Quantity (mg/tablet)</b>
COMPOUND 24	10
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	
	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	<u>1.0</u>
Total	100 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The

5 SCMS, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

	<b>Quantity (mg/suppository)</b>
COMPOUND 24	20
Saturated fatty acid glycerides	<u>2,000</u>
Total	2,020 mg

10

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

15 An intravenous formulation may be prepared as follows:

	<b><u>Quantity</u></b>
COMPOUND 24	10 mg
isotonic saline	1000 mL
glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

5 The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

10 The scope of the invention is not to be limited by the description of the examples. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

15 Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented by way of example.